BEHAVIORAL PHARMACOLOGY AND TOXICOLOGY[1]

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If a survey of behavioral pharmacology and toxicology in the seventies must be a review, rather than an extensive treatise, it must be limited to a fraction of the relevant topics. The reader who is skeptical of conventional caveats and apologies can peruse the six volumes that make up just one third of the new *Handbook of Psychopharmacology* (1) or count the references in papers on drugs, CNS functions, and behavior that have appeared in this and related serials since the general reviews by Weiss & Laties (2), Himwich & Alpers (3), and Kumar, Stolerman & Steinberg (4). In fact, the original plan of this paper included a fairly broad range of topics, and also a review of reviews on various aspects of psychopharmacology and behavioral toxicology. However, the sheer size of the materials collected,[2] hundreds of references to reviews and books in various areas of neuropsychopharmacology, only for the period from 1970–1975, required the elimination of the general reference section. Furthermore, the psychopharmacology section had to be limited to drug-behavior interactions obtained in recent years with barbiturates, benzodiazepines, and 5-hydroxytryptamine (5-HT) system agents that have an antipunishment action. Finally, the behavioral toxicology section has been devoted mainly to two lines of work that have considerable interest from both a methodological and a theoretical viewpoint: to some aspects of the stimulus functions of drugs and to some of the effects of drugs and other chemicals on behavioral development.

[1]Generic names of drugs were used whenever possible. US adopted names have been used where several generic names are extant. When no generic names were available, well-known (abridged) chemical names were adopted. When used more than once these were replaced by common abbreviations indicated in the text.

[2]The literature survey pertaining to this review was concluded at the end of May 1975. The survey was greatly facilitated by the material received from several colleagues in different countries, who were asked to send reprints, preprints, and information on work being prepared for publication.

This introduction must be extended by a brief discussion of the philosophies underlying various approaches in neuropsychopharmacology, which are not obvious to the nonspecialist. On the one hand, it is not difficult to understand the rationale of increasingly sophisticated screening programs, which attempt to assess the properties of new agents, or that of studies concerned with correlations between behavioral and physiological-biochemical events. On the other hand, it is sometimes difficult to accept the hard fact that most of the interactions between treatments and several organismic and test variables are not presently amenable to explanations in physiological-biochemical terms. As a consequence, considerable efforts are required to establish provisional models of drug action in behavioral terms.

The analysis that follows considers in some detail two approaches leading to data of considerable interest. The first can be broadly categorized as a functional analysis of behavior changes induced by treatments. In fact, this approach uses a wide variety of response outputs generated mainly by schedules of intermittent reinforcement in order to identify the variables that can influence either size or direction of drug-induced changes. The second makes use of provisional models of behavior organization in terms that are neither strictly functional nor strictly physiological, but intermediate between the two; in other words, it makes recourse to so-called assumed processes or mechanisms in the analysis of input-output relationships (and of drug effects thereon). Of course, both the above distinction and that between physiological-biochemical and behavioral models are far from rigid. Nevertheless, there still remains a substantial difference between a functional analysis saying, "These effects of amphetamine are amenable (or not amenable) to a rate dependence model" (see below) and an analysis saying, "These same effects of amphetamine are suggestive of an attentional (or a motor, or a motivational, or an associative) bias." On the other hand, both behavioral approaches make use of a wide variety of effects in different, or even opposite, directions. When these are obtained with the same drug and different experimental contingencies (or by measuring different outputs given a particular contingency) the inevitable result is a complex (interactionist) model of drug action. This is not easily reconciled with a brain-behavior (correlational) approach, because even simple drug-behavior interactions have not yet been accounted for in physiological-biochemical terms (e.g. the opposite effects of amphetamine on locomotor and on some "exploratory" activities).

BARBITURATES, BENZODIAZEPINES, AND 5-HT SYSTEM AGENTS

Any discussion of psychotropic drug effects should start with a summary of studies concerning "unlearned" behaviors—spontaneous activities of various kinds, feeding and drinking responses, sexual and social responses—and then go on with data on stimulus reactivity, habituation, and operant behaviors maintained by sensory reinforcement (e.g. illumination changes) and by intracranial reinforcement (self-stimulation). This approach, however, would make it impossible to deal in any detail with studies that can best illustrate the complexity of drug-behavior interactions. Therefore, the following sections deal with drug effects on responses controlled by sched-

ules of positive reinforcement, on differential response (discriminations), on behavior suppressed by punishment, on response maintained by negative reinforcement (escape-avoidance), and on changes in response caused by nonreinforcement (extinction, frustrative nonreward). Finally, an attempt is made to analyze some of the evidence on drugs that share one of the important properties of barbiturates and benzodiazepines (the antipunishment action), namely, 5-HT depletors and antagonists.

Operant Schedules with Positive Reinforcement

A well-known review published by Kelleher & Morse in 1968 (5) pointed out the uselessness of labels such as *stimulant* and *depressant drugs.* In fact, the results obtained with operant schedules[3] showed a series of remarkable analogies between amphetamine, on the one side, and barbiturates and benzodiazepines (or even neuroleptics), on the other, consisting mainly of similar rate-dependent changes in various situations. A well-known example can be drawn from fixed-interval (FI) schedules, in which several agents can increase the low rates observed in the early portions of the intervals (i.e. when a considerable delay separates the experimental subject from the next available reward), and reduce the high rates observed later in the same intervals. Of course, Kelleher & Morse (5) also pointed out that rate dependence cannot be put on a par with the laws of physics and chemistry, as exemplified by critical differences between barbiturates and benzodiazepines—enhancing low rates in the presence of a punishment contingency—and amphetamine, having either slight or no antipunishment effects.

In recent years the study of barbiturate and benzodiazepine effects on behaviors controlled by schedules of positive reinforcement has been extended in several directions. In the first place, previous reports of a relative insensitivity to drug of high and regular rates generated by small- and medium-sized fixed ratios (FRs) have been ascribed to the insufficiency of the measurements made before computers became available (7). In fact, a fine-grain analysis of pentobarbital effects in pigeons showed a consistent reduction of postreinforcement pauses and an increased cohesion of response patterns, two changes in good agreement with each other, with enhancements of low rates reported previously, and with the antisatiety effects of several barbiturates. The use of FRs of increasing size indicated a greater persistence of response in spite of less and less favorable reinforcement contingencies after administration of phenobarbital or chlordiazepoxide to pigeons (8). Furthermore, rats performing in extended FR sessions were employed to assess interactions between drug treatments and behavior changes induced by satiation. Interestingly enough, out of several agents that were able to increase response controlled by other schedules, phenobarbital, meprobamate, and chlordiazepoxide showed an antisatiety action, while diazepam did not, and oxazepam worked in the opposite direction (9, 10). On the other hand, unexplained differences between the effects of various

[3]No attempt can be made here to describe the schedules mentioned. While the standard reference must remain the textbook by Ferster & Skinner (6), much essential information can be found in condensed form in the review by Kelleher & Morse (5).

benzodiazepines on variable-interval (VI) response in rats appeared also in a study comparing several compounds. Only oxazepam gave a conventional profile—rate increases at low doses and rate decreases at higher doses—while only rate decreases reached statistical significance after chlordiazepoxide and diazepam, and no changes were observed over a wide dosage range with temazepam (11). One could speculate here that the use of schedules generating borderline rates (lower than those that are easily increased and higher than those that can be only decreased) could be exploited to analyze further subtle differences within a given drug category. In fact, another study showed few, if any, enhancing effects on FI response after chlordiazepoxide, inconsistent enhancements after diazepam, and marked enhancements after phenobarbital (12). As concerns benzodiazepines, these data obtained with pigeons, in contrast with those obtained in similar schedules either in the same or in different species (5, 13), indicate that the analysis of treatment and test factors interacting to produce widely differing changes in response is far from complete.

The rate dependence of pentobarbital effects in pigeons was further confirmed by the use of conjunctive FR-FI schedules. However, given the same baseline rate, drug-induced enhancements of FR response were less marked than those of FI response when the two components were scheduled on separate keys (14). Furthermore, reductions of high FR rates in pigeons, also after pentobarbital, were found to be about the same in multiple and in mixed FR-FI schedules, while high (terminal) FI rates appeared more resistant to reduction in mixed, than in multiple schedules (15). These interactions led to a discussion of treatment effects as a function of stimulus control of behavior, especially because a well-known study had shown an attenuation of the typical effects of pentobarbital on FI response in pigeons when the behavior was under the control of a succession of exteroceptive stimuli (so-called FI with superimposed clock) (16). In a recent study, also using pigeons, indentical VI periods were associated to different key colors, leading to substantial differences in response rates in spite of identical contingencies in various portions of the schedule. These differences were markedly reduced by diazepam, due mainly to rate enhancements during the presentation of the less preferred colors (green, yellow, and red) after 0.62 and 2.5 mg/kg, and to a rate reduction during the presentation of the favorite color (blue) after a higher dose (5 mg/kg) (16a). In another investigation, again with pigeons, even-numbered minutes in a long FI went with a stimulus identical with that presented when food was delivered (S^D), while odd-numbered minutes went with one or the other of several stimulus conditions never associated with food delivery (S^Δ). Enhancements of low rates were obtained with amobarbital in the presence of both types of stimuli, but they were less marked in some of the S^Δ conditions apparently exerting a strong inhibitory control (17).

Complex manipulations of the relationships between stimuli, responses, and reinforcements were also performed in a study on pigeons, in which one component of a multiple VI-VI schedule was substituted either by VI with a prereinforcement signal (which led to marked response reduction in the VI + signal component, and to a marked response enhancement in the regular VI component), or by administration of gratis food at irregular intervals, variable time (VT), which led to a marked

rate reduction in VT itself, and to a moderate reduction in the regular VI component. This study allowed a striking separation between the effects of amphetamine, which lost its ability to enhance low rates, and those of phenobarbital, which maintained such ability both in VI + signal and in VT (18).

Equally interesting results were obtained by measuring not only schedule-controlled responses, but also schedule-induced (adjunctive) responses, that is, behaviors such as drinking an excess amount of water that can develop upon exposure to schedules of intermittent reinforcement. For example, a study showed that adjunctive licking could remain basically unaffected after doses of pentobarbital and amphetamine, which increased response in second-order schedules (19). An experiment showed that the development of adjunctive drinking can take place at a normal, or even at a higher rate during the chronic administration of chlordiazepoxide (19a). Another study measured both schedule-controlled and adjunctive components of the same output—licking on a FI schedule by rats—and showed a remarkable insensitivity of the latter to chlordiazepoxide at doses that induced substantial increases of the former (20). The same study also revealed differences between chlordiazepoxide and amphetamine, since both schedule-controlled and adjunctive responses were insensitive to the latter agent until depressant effects appeared at higher doses. Somewhat different results were obtained in a study with squirrel monkeys, which used the same FI contingency and showed chlordiazepoxide enhancements of both schedule-controlled lever pressing and schedule-induced water or ethanol consumption (21).

Additional differences in drug profiles were obtained by extending operant studies to mouse responses in a multiple FR-FI schedule. A preliminary report of this work suggests that amphetamine has conventional effects (enhancement of low FI rates and reduction of high FR rates), while both FI and FR response enhancements are indicated for pentobarbital (22). Regarding schedules with differential reinforcement of low rates (DRL), previous studies showing enhanced response frequencies and reduced reinforcement frequencies after barbiturates and benzodiazepines were replicated with similar results in the same and in other spaced-responding schedules (23–25). However, response-enhancing effects of chlordiazepoxide (and also, of amphetamine) were negligible or absent in a study with pigeons, while higher doses of both agents were able to reduce response rates (26). Another remarkable exception to drug enhancement of responses emitted at low rates was obtained by superimposing a classical alimentary stimulus (i.e. a signal paired with gratis food) during VI sessions, leading to a suppression similar to that induced by classically conditioned aversive stimuli. No attenuation of such suppression was obtained with chlordiazepoxide and with diazepam in rats and monkeys, while additional tests limited to chlordiazepoxide and to rats showed a drug disinhibition of responses suppressed by a fear signal (see below). Symmetrically opposite results were obtained with amphetamine, which enhanced low rates during the presentation of classical alimentary CS, but not during the presentation of classical aversive CS (27).

In summary, recent work with operant schedules has shown (*a*) several important differences both within and between drug groups, (*b*) several differences in rate-

dependence functions obtained with given drugs, due to differences in test variables including those that affect stimulus control of behavior, and (*c*) some remarkable exceptions to the rate-dependence phenomenon, to be discussed again in a later section.

Experiments on Discriminations

Several experiments with either discrete-trial or operant discriminations were carried out in an attempt to answer particular questions, that is, should the disruption of differential response by barbiturates and benzodiazepines be ascribed to (*a*) a general psychomotor depression (overall response reduction, leading to a relative increase of incorrect responses), or to (*b*) attentional, associative, or motivational changes (parallel decreases of correct responses and increases of incorrect responses), to be further separated from each other by appropriate control experiments, or (*c*) an impairment of response control (selective reappearance of previously suppressed responses)? Although most data on aversively motivated behaviors are not examined until later, the following discussion must consider several results obtained with alimentary and defensive discrimination tasks. A fairly large portion of the available data on discriminations (28–33)—to be considered in conjunction with (*a*) the enhancements of low rates in operant schedules (see above) and (*b*) the enhancements of avoidance and extinction rates (see later sections)—apparently supports a response disinhibition model of benzodiazepine and barbiturate effects. A closer analysis of the data, however, shows a wide variety of interactions between treatment factors and species, stimulus, response, and other experimental factors. In some instances the results were only superficially in contrast with a disinhibition hypothesis since, for example, one can easily understand why an impairment of response control should lead to more marked changes in a successive, than in a simultaneous discrimination (28).

In other instances treatment factors seem to dominate the picture, as in a series of experiments on delayed matching in which both the presence or absence of an influence of the delay factor, and the balance between "go" (omission) and "no go" (commission) errors, depended on the agent used. Disinhibitory phenomena seemed to be absent in the case of several barbiturates, while mixed profiles of remarkable complexity were obtained with various benzodiazepines (34, 35). Furthermore, several studies using vigilance (signal detection) tasks with either positive or negative reinforcement gave variable ratios of "go" and "no go" errors after secobarbital in monkeys, as shown by the data reported in (36, 37) and in several previous papers quoted therein. Because omission errors accounted for most, if not all, of the disruption observed with chlorpromazine, it can be shown that the variability of the barbiturate profile should be considered as a genuine drug-task interaction, rather than as a consequence of differences between tasks per se.

The present discussion cannot be extended to include all available experiments, for example those concerning repeated acquisition of response chains (38, 39, 39a), those on discrimination behaviors requiring a joint use of exteroceptive and response-produced cues (40, 40a), those on discrimination of the pressure exerted on an operandum (41), and those on alternation behaviors (42, 43, 43a). However, the

above and several other results indicate that drug-induced changes of differential response are not amenable to simple models such as disinhibition or rate dependence. This is also shown by studies finding improved differential response after amobarbital (44) and after chlordiazepoxide (45), due to a selective reduction of lever presses during nonreinforced signals. Finally, it must be emphasized that the above inconsistencies cannot be explained by using higher or lower cost of incorrect response as a criterion of classification. In fact, a closer analysis of the above and of several previous studies would reveal that presence or absence of given changes, for example response disinhibition, cannot be related systematically to the consequences, at the reinforcement level, of inappropriate response.

An analysis of discriminative functions of barbiturates and benzodiazepines (state-dependent learning) is outside the scope of this discussion, especially since the reader can be referred to several recent papers and reviews in (46, 47). It can only be mentioned here that dissociation phenomena caused by transitions from the drug to the no-drug state, or vice versa, have been repeatedly exploited in experiments on habit reversal. Interestingly enough, state changes facilitated the acquisition of behavior incompatible with that established previously not only in several experiments using presession treatments (48–54), but also in a study using one-trial discrimination learning and treatments administered immediately after the first exposure (55). Another line of work to which considerable efforts were devoted in the sixties [see (56, 57) and the papers quoted therein] regards the tranquilizer prevention of "fixations," that is, those stereotypes that are caused by exposure to insoluble problems and that interfere with discrimination learning when the problem is made soluble. Benzodiazepine effects in situations causing "neurosis" have also been investigated by tests in which monkeys become inactive (58), or in which rats make an increasing use of an escape ("time out") platform (59), when discrimination is made more and more difficult. Treatment with diazepam (58) or with chlordiazepoxide (59) was found to facilitate discrimination by reducing the above phenomena. Both fixation induced by exposure to insoluble problems in the Lashley jumping stand (56, 57) and neurosis triggered by increasingly difficult discriminations between signals corresponding to reward and punishment (58, 59) are generally ascribed to the high aversiveness of the situation. Therefore, the above effects appear to be directly related to the antipunishment properties discussed in the following section. Drug studies exploiting lack of adaptation to experimental contingencies are not limited to paradigms that mimic those originally used in the famous experiments by the Pavlovian school. For example, dogs of a "genetically nervous" strain with low performances in a simple bar-press task with food reinforcement showed operant rates similar to those of a "stable" strain after treatment with chlordiazepoxide (60). The authors of this study, however, have emphasized "the superficial nature of the improved behavior," based on the fact that most of the animals stopped bar pressing and assumed rigid ("frozen") postures within two days after medication withdrawal (60a).

In summary, from the considerable amount of work on discrimination some firm conclusions can be drawn concerning facilitation of habit reversal by state changes, and facilitation of discrimination behavior disrupted by events that can be classified

as aversive. On the other hand, little progress has been made in the understanding of mechanisms responsible for drug effects on several types of discrimination—an uncomfortable conclusion indeed, if one considers that these compounds are used not only as sedative-hypnotics, but also at times when people must engage in their regular activities.

Behavior Suppressed by Punishment

When considering the most popular types of barbiturate and benzodiazepine effects —those on behaviors modified by punishment (present section) and those on behaviors maintained by negative reinforcement (next section)—one quickly discovers that the simplified "antiemotional" explanations that prevailed until about the midsixties have been seriously questioned over the past few years. However, at least one category of effects has withstood experimental testing in a wide variety of different situations, namely, the drug attenuation of the suppression of ongoing behaviors by response-contingent punishment (5, 61, 62). It is well known that this antipunishment effect, which is best shown by approach-avoidance (Geller type) schedules, cannot be ascribed to an antinociceptive action of barbiturates and benzodiazepines. This is shown by the negative results obtained with potent analgesic agents (5), and also by recent results indicating that the size of the analgesic action of chlordiazepoxide in spatial preference and titration tests is much less than that of its antipunishment action (63, 64).

Barbiturate and benzodiazepine effects on behavior suppressed by response-contingent punishment have been confirmed by a great number of studies published over the past few years, most of which cannot even be listed with the literature cited. Some of these studies must be mentioned because they made accurate comparisons of rate-dependent effects on punished and unpunished behavior (13, 65–67), or analyzed interactions between treatment and other factors such as punishment intensity (68), or took into account nonmonotonic (Kamin type) response changes in the first 24 hr after punishment of an approach response (69). Other studies provided indications on central sites of action by showing that oxazepam given systemically could alleviate the intensified suppression caused by localized cholinergic treatment of the hypothalamus (70) and of the dorsal raphe (71). Several experiments obtained changes in the expected direction by a variety of methods, such as a simplified test measuring punishment effects on licking responses (66a, 72), discrete-trial approach-avoidance tasks with either shocks (73) or air blasts (74) as the punishing events, and maze tasks in which performance tends to deteriorate with heating of the floor (75).

Antipunishment effects usually measured in rats, pigeons, and monkeys have also been observed in goldfish treated with phenobarbital (76) and in pigs treated with diazepam or with phenobarbital (77, 77a), while the effects of chlordiazepoxide were surprisingly small in the latter species (78). A study pointed out that antipunishment effects obtained with amobarbital, normally disappearing upon abrupt discontinuation of treatment, can be carried over to the no-drug state if the drug is withdrawn gradually (79). By the use of repeated treatments it could be shown that no tolerance to oxazepam develops with respect to antipunishment properties, while depression

of unpunished behavior can be rapidly attenuated (80). A similar result was obtained by using flurazepam at doses sufficient to depress unpunished response, and exerting little effect on punished low rates. Repeated treatments led to an attenuation of the response suppression, and to an appearance of a marked antipunishment action (81). Analogies and differences between drugs were repeatedly investigated. For example, a study using rats showed chlordiazepoxide enhancements of both unpunished and punished responses over a fairly wide dosage range, while a strong tendency toward reduction of unpunished VI rates by pentobarbital was paralleled by a slight antipunishment action (82). On the other hand, no substantial differences between the antipunishment effects of the two drugs were observed in a study using pigeons, in which the treatments also exerted similar effects on unpunished behavior (66).

As illustrated in the above-mentioned review by Kelleher & Morse (5), behavior suppression by stimuli paired with noncontingent shock is not alleviated by barbiturates and benzodiazepines as consistently as suppression by contingent shock. Furthermore, the same reviewers hypothesized that the former type of suppression might be substantially insensitive to drugs, while disinhibition, when observed, could perhaps be ascribed to adventitious punishment phenomena. In fact, positive results had been obtained by the use of short intervals between the conditioned stimulus (CS) and the unconditioned stimulus (UCS), that is, in situations in which noncontingent shock can be easily "perceived" as if it were response-contingent. This type of explanation has been rejected by Millenson & Leslie in a paper that provides several of the more recent references (83). These investigators have attempted to show that the apparently inconsistent results obtained in tests with noncontingent shock were due either to the treatment schedules (acute treatments more effective than chronic treatments) or to the procedures used for the measurement of classically conditioned emotional responses (CERs) (operant and instrumental outputs more sensitive to drug than consummatory outputs). Assuming for a moment that these criteria of classification have general validity, several problems would still remain without solution. In fact, it would be difficult to understand why the use of chronic treatment schedules, or of consummatory behaviors, should allow the drugs to exert disinhibiting effects in the case of response-contingent shock (see several of the papers quoted above), while leading to inconsistent, or even to opposite (paradoxical) effects (84) in the case of CER situations, not to speak of the inconsistencies between studies comparing drug effects on CER acquisition and performance (85, 86).

Some recent experiments have shown a benzodiazepine attenuation of suppression in CER tests using both short (27) and long (87) CS-UCS intervals. The latter study used overtrained animals with well-developed "inhibition of delay"—or "temporal discrimination"—i.e. with normal or near normal response rates at the beginning of the CS presentation period and an increasing suppression in successive portions of the 5-min CS-UCS interval. A breakdown of the data revealed a rate dependence of oxazepam effects, because high rates in the initial portions of the intervals were reduced while low rates in later portions were increased. An effort was also made to compare more directly the effects of drugs as a function of presence or absence of a response-shock contingency, which was achieved by using pigeons performing

in a FI schedule (88). Some of the animals received response-contingent shocks, while others were "yoked" to the former ones so as to receive noncontingent shocks. Both pentobarbital and chlordiazepoxide produced the expected attenuation of suppression with the punishment procedure, while only pentobarbital was effective in yoked animals. A similar experiment used rats performing in a VI schedule, and showed much larger disinhibiting effects of chlordiazepoxide in the animals punished with response-contingent shock, than in those receiving noncontingent shock (88a); (this study must also be recommended for a concise analysis of the mechanisms that may be responsible for different consequences of contingent vs noncontingent shock). Finally, one can mention here a study that made use of an insufficiently exploited sensitization phenomenon, namely, the enhancement by prior exposure to strong noncontingent shock of the suppressant effects of mild contingent shock. By treating animals during the initial shock exposure it was shown that the dose of pentobarbital required to prevent sensitization was quite high, at least when compared to those that are sufficient to disinhibit punished response (89).

The above picture is further complicated by passive avoidance and classical conditioning studies other than those measuring the suppression of ongoing alimentary responses. As concerns the former, disinhibiting effects were obtained with several benzodiazepines and barbiturates (90–92). One of the studies, however, showed by appropriate controls that the chlordiazepoxide impairment of passive avoidance should be largely ascribed to state-dependence phenomena (92). Two studies measured activity in a Y maze and passive avoidance of the arm in which rats had previously been shocked (note, however, that this initial shock exposure had not been made contingent upon entry into the arm itself). Passive avoidance was attenuated both by amobarbital (93) and by chlordiazepoxide (94), but its extinction was either unaffected or retarded. Passive avoidance of "naturally" fearful situations was attenuated by benzodiazepines and barbiturates in the case of an elevated (open-side) arm test in a Y maze, but not in the case of a brightly illuminated arm test (95, 96). A marked disruption of rat passive avoidance was also found with posttrial pentobarbital treatment. The appropriate controls, however, showed that this effect was due to a retrograde state-dependent learning similar to what has been mentioned when speaking of facilitation of habit reversal by changes of state (55, 97, 98). Finally, an experiment exploited the disturbances of rat passive avoidance that are caused by changes in the illumination cycle. The effects of chlordiazepoxide administered in the drinking water were mainly in the direction of an accelerated recovery of passive avoidance abilities after phase shifts (99).

As concerns responses to classically conditioned fear stimuli the sole purpose of comparing drug effects on a wide variety of different outputs can be that of showing the slight heuristic value of terms such as "antiemotional (antifear) action." Overt responses of rats to buzzers previously paired with shock were markedly reduced by chlordiazepoxide and by phenobarbital (100). Several motor and autonomic responses elicited in cats by clicks paired with aversive midbrain stimulation were attenuated by chlordiazepoxide and by nitrazepam (101). A study showed a chlordiazepoxide reduction of classically conditioned (nictitating membrane) responses

in rabbits (102). On the other hand, the same group showed that treatment prior to tone-shock pairings did not prevent the CS from acquiring avoidance-enhancing properties (103). A similar result was obtained in rats with exposure to CS-UCS pairings in the no-drug state, followed by treatment sessions in the amobarbital state in which the effects of the classical CS on avoidance response were measured in an extinction paradigm (104). Such maintenance of the response-enhancing properties of classical CS both in a drug-no-drug (103) and in a no-drug-drug (104) paradigm excludes both an antifear effect of the drugs used, and a state-dependence explanation of the failure to obtain significant deviations from the controls. Interestingly enough, the latter experiment was paralleled by another study in which a stimulus previously paired to amobarbital treatment was able to exert a depressant effect on active avoidance response (105).

In summary, several data show that barbiturate and benzodiazepine effects in situations with either contingent or noncontingent exposure to aversive events cannot be explained on the basis of one-factor models of drug action. Many of these data open the door to a more systematic analysis of interactions between treatment factors (different drugs, acute versus chronic schedules), organismic factors (species and strains), and test factors such as operant (instrumental) versus consummatory ongoing behaviors, CS modality and intensity, UCS duration and intensity, temporal relationships between CS and UCS, and of course presence versus absence of a response-shock contingency. Several factors that can favor, or prevent, the transfer of drug-induced changes from the treatment to the no-treatment state should also be investigated by acquisition and performance experiments and by different schedules of treatment withdrawal, given the interest of these phenomena in human psychopharmacology.

Behavior Maintained by Negative Reinforcement

The experiments on behaviors maintained by negative reinforcement have provided much evidence that is again incompatible with unqualified antifear models of barbiturate and benzodiazepine action. Most of the earlier studies, which cannot be reviewed here, had shown that active avoidance depression by these agents, even when not entirely ascribable to sedation or to motor incapacitation, was far from being as selective as the one obtained with phenothiazines and butyrophenones. Some of these earlier studies using operant escape-avoidance techniques had already pointed out a complex profile of rate increases and decreases after drug treatments, mostly in agreement with a rate-dependence model (106). A more recent study used monkeys performing in a multiple VI escape schedule with response termination of noise paired to irregularly pulsed shock in one component, and response termination of continuous shock of low intensity in the other component. In agreement with previous results denying a specific antiavoidance action of benzodiazepines, chlordiazepoxide was found to be more effective in reducing response rates in the latter, than in the former component of the schedule (107).

On the other hand, many experiments carried out over the past decade have shown that several barbiturates and benzodiazepines, when given at doses lower

than those endowed with an antiavoidance action, can facilitate the acquisition and/or the performance of two-way (shuttle box) and lever-press avoidance responses (81, 108–121). Furthermore, some experiments carried out in parallel with one of the two-way studies mentioned above showed no effects of chlordiazepoxide on the acquisition of one-way avoidance and a depressant action of the same drug on the acquisition of pole-climbing avoidance (119, 122). The attempts to explain the avoidance facilitation obtained in particular situations have generally made recourse to models emphasizing drug effects on suppression phenomena that interfere with active response. (These are ascribed to the general aversiveness of the tasks, to the confounding of safe and unsafe parts of the apparatus in bidirectional tests, and to adventitious punishment of outputs that are just about to fulfill a response criterion when a scheduled shock is turned on.) In other words, facilitation is explained by a greater drug influence on response suppression, than on response activation, in agreement with the fact that antipunishment effects have repeatedly been shown to be more specific than antiavoidance effects.

Given the variable balance between activation and suppression phenomena in apparently similar avoidance tasks, leading to different acquisition rates and performance asymptotes, one could disregard several failures to show a facilitation, which have been reported in references 103, 123, and 124. Surprisingly enough, however, some experiments showed an absence of two-way avoidance facilitation with a drug effective in other experiments mentioned above (amobarbital), and in conditions allowing the appearance of response enhancements after treatment with a nonbarbiturate sedative (methylpentinol) (125, 126).

Several data should be analyzed in detail in order to account for at least part of the variability in avoidance changes, such as the interactions between treatment and strain factors in a mouse study using both active and passive avoidance (91); the drug modification of repertoires elicited by shock (127); the drug depression of pseudoconditioned response with unpaired presentations of noise and shocks (128); and the interactions between treatment and stimulus factors, allowing a drug facilitation in the presence, but not in the absence, of stimulus events providing a response feedback (109). Furthermore, state-dependence phenomena have been shown to vary from one situation to the other (109, 111, 112, 117, 119, 122, 129–131). When present, they consisted sometimes of symmetrical decrements with changes of state in either direction, and sometimes of an asymmetrical dissociation with decrements after drug-no-drug transitions, but not after no-drug-drug transitions. Complex interactions between treatments (drugs and doses), test factors (responses, use of special procedures such as forced extinction by flooding), and state-dependence phenomena should also be analyzed to understand a wide variety of drug effects on extinction of avoidance, for which the reader must be referred to the original studies (104, 119, 122, 132–136).

Finally, several experiments conducted in recent years have dealt with drug effects on heart rate, respiratory rate, blood pressure, temperature, and urine excretion in animals performing escape-avoidance tasks or exposed to classical contingencies (137–141). In agreement with the data showing a drug-induced reduction of plasma

corticosterone changes upon exposure to nonspecific stress (142) or to escapable shock (143), these studies have pointed out an attenuation of the above responses by barbiturates and benzodiazepines. By consulting the original papers, however, the reader will quickly discover that the authors disagree with respect to relative effectiveness of drugs on specified motor outputs, such as avoidance and classically conditioned responses, and on other outputs.

In summary, the results concerning behaviors maintained by negative reinforcement support the conclusions outlined in the previous section. Many data suggest that avoidance facilitation can result from the attenuation of punishment suppression. Other data confirm that the relations between antipunishment and other drug effects are still poorly understood, while the evidence on interactions between treatment factors, response and other test factors, and state-dependence phenomena provides the basis for testing multifactorial models of drug action.

Changes in Positively Reinforcing Events: Extinction, Frustrative Nonreward, and Incentive Shifts

Experimental manipulations of positively reinforcing events have been shown to cause a wide variety of response changes, as shown by the extensive literature on extinction, frustrative nonreward, and incentive shifts. In particular, several theorists support the view that nonobtention of anticipated ("expected") rewards leads in the first place to emotional changes (frustration reaction), and in the second place to conditioning phenomena by which nonreward-related stimuli acquire control over instrumental or operant responses (144, 145). In order to simplify the discussion of drug-induced changes one can add here that several phenomena have been ascribed to the above processes, namely, (*a*) the higher running speeds observed during acquisition (particularly in the second part of it) with partial reinforcement (PRF) than with consistent reinforcement (CRF) (the partial reinforcement acquisition effect, PRAE); (*b*) the greater resistance to extinction after PRF than after CRF (the partial reinforcement extinction effect, PREE); (*c*) the greater running speed in the second alley of an apparatus with two goal boxes when an anticipated reward is missed in the first box (the double alley frustration effect, DAFE); and (*d*) the tendency to escape from a situation in which an anticipated reward is missed (escape from frustration, EFR). Given the above theoretical framework, and the resulting "fear = frustration hypothesis," it is not surprising that runway tests, or their operant equivalents, have often been used to confirm the antiemotional effects of benzodiazepines and barbiturates and also, after such effects are considered proved, to achieve a separation between emotional and nonemotional phenomena in PRF and other experiments with manipulation of reinforcing events.

Since two well-known studies published in the early sixties, showing respectively an antiextinction (146) and an anti-PRAE (147) effect of amobarbital in rats, several experiments with barbiturates and benzodiazepines, also using rats, have yielded results supporting the above assumptions. This applies to the drug retardation of extinction (148–154), to the attenuation or disappearance of the PRAE (155, 156), and to the attenuation of EFR (155). Furthermore, the drugs were found to prevent

the response attenuation caused by a reduction of reward magnitude (157–159), while the response depression caused by reinforcement withdrawal in a discrete-trial lever-press task was antagonized by chlordiazepoxide, but not by phenobarbital and pentobarbital (160). A control study showed no drug influence on response enhancements caused by an increase of reward magnitude, thereby excluding the possibility that the above results might be ascribed to an impaired perception of changes in reinforcement size (161). A more complex experiment exploited response enhancements and reductions caused by signals paired to incentive shifts in opposite directions, and showed differential drug effects essentially similar to those outlined above (162).

From a certain point on, however, the results of both nonpharmacological and pharmacological experiments created a situation of an amazing complexity. Frustration models were substantially modified by theorists who emphasized the variable balance between emotional (aversive) and nonemotional (perceptual-cognitive) consequences of PRF, based mainly on experiments with different sequences of reward and nonreward (163). Alternative explanations of PRF consequences were also provided, based mainly on the finding that nonobtention of anticipated reinforcements can lead to opposite changes in consummatory outputs (depressed) and instrumental outputs (enhanced) (164).

On the pharmacologist's side, some experiments with barbiturates found either a minimal effect on extinction (44) or a decreased resistance to extinction (165), with complex interactions depending on schedules of treatment and of drug withdrawal (abrupt versus gradual) (166). A control experiment showed that this paradoxical acceleration of extinction was to a large extent independent of state changes (165). Another study using chlordiazepoxide showed the expected increase of response in extinction, but the drug was unable to affect the changes in response force (167). Furthermore, benzodiazepine effects on extinguished behavior have been far from consistent (65, 66a, 67). Repeated attempts to interfere with the DAFE by amobarbital treatment resulted in clear-cut failures (155, 168–171), while one success was scored by using rats made dependent on barbital (172). A drug attenuation of the PREE was demonstrated in animals trained without drug and extinguished with drug, but not in animals trained and extinguished in the drug state, while variable results were obtained with animals trained with drug and extinguished without drug (150, 151, 154, 155, 169). Therefore, few conclusions could be drawn concerning the relative role of drug effects on PRF consequences and of state-dependence phenomena. Finally, the complexity of the results obtained prevents a detailed analysis of a remarkable series of amobarbital studies concerning PRF and CRF with different spacing of trials (173), the PREE following a limited acquisition experience (174), different magnitudes of consistent reinforcement (175), and treatment schedules based on sequential hypotheses (differential effects of drug given either before nonrewarded trials followed by rewarded trials, or before rewarded trials followed by nonrewarded trials) (176). At this point the reader must be referred to a recent review that attempts to reconcile several of the above inconsistencies with the notion of an antiemotional mechanism of action of barbiturates and benzodiazepines (176a).

Speculations on the Nature of Drug-Behavior Interactions

A discussion of some of the factors that may influence the size, or even the direction, of barbiturate and benzodiazepine effects can exploit selected data obtained with agents that are known both for their rate-dependent effects and for their different profiles with respect to feeding and drinking responses. In fact, these consummatory behaviors are uniformly depressed by amphetamine, while they remain unaffected, or are enhanced, after barbiturate and benzodiazepine treatments (except, of course, at doses that cause heavy sedation and motor impairment). Given these differences, one can consider enhancements of low response rates as a function of response consequences at the reinforcement level. A hypothesis that response cost per se discriminates between drug profiles is quickly disproven by several data showing amphetamine, barbiturate, and benzodiazepine enhancements both in the absence, and in the presence of a reduction of reinforcement frequency (e.g. FI versus DRL schedules) (5). On the other hand, a striking attenuation of amphetamine changes has been observed sometimes when measuring "operants" drawn from the consummatory repertoire, such as FI-licking by rats (20), or when measuring responses with mixed consummatory and preparatory (instrumental) properties controlled by schedules with adverse consequences of hyperresponse, such as DRL key-pecking by pigeons (26). Furthermore, enhancements of low rates by chlordiazepoxide have been found when measuring FI-licking (20), that is, when the operant was drawn from the consummatory repertoire and the schedule was without adverse consequences of hyperresponding. In contrast, the usual effect of the same drug on DRL was at least markedly attenuated when key-pecking responses of pigeons were studied (26). Finally, the contrasting profiles of amphetamine and of barbiturates and benzodiazepines on punishment suppression were reversed in experiments on suppression by stimuli paired with gratis food, which are known to elicit classically conditioned consummatory responses at the expense of ongoing instrumental behavior (177). In such a situation, amphetamine-treated animals resumed operant response, while benzodiazepine-treated animals did not (27).

A more detailed analysis should consider several other data showing exceptions to the absence of antipunishment effects in amphetamine-treated animals, exceptions to the antipunishment properties of barbiturates and benzodiazepines, and also, exceptions to the exceptions (e.g. instances in which amphetamine enhanced responses drawn from the consummatory repertoire). Nevertheless the above data, when considered with the complex effects of barbiturates and benzodiazepines on extinction and frustrative nonreward, suggest that several types of interactions have not been sufficiently explored. Some of the critical factors, taken one by one, have indeed received much attention; for example, the differences between drugs belonging to the same class in particular situations; the different "reversal points" in nonmonotonic dose-response functions, depending on the test used; and quantitative differences in rate-dependence functions, depending on the schedule. Others seem to offer much space to future investigations, as suggested by the above interactions between (*a*) treatments that enhance, or depress, consummatory outputs; (*b*) responses drawn from different components of a species-specific repertoire (mainly

preparatory, or mainly consummatory, or with mixed properties as in the case of bird pecks); and (*c*) schedules generating low rates either with, or without, adverse consequences of hyperresponse at the reinforcement level. Drug effects as a function of stimulus control of behavior are also amenable to a similar analysis.[4] In fact, nonpharmacological studies designed to maximize the separation between "consummatory" and "instrumental" properties of stimuli have shown that the two types of signals can elicit entirely different types of response changes in the dog (177). (Of course, this divergence is facilitated by the fact that instrumental and consummatory activities are more easily separated from each other in the dog than in other laboratory animals.) Finally, the finding (also in dogs) of opposite effects of partial reinforcement on consummatory activities (depressed) and on instrumental activities (enhanced) shows that alternative models of nonreward consequences (164) and of drug effects thereon must be explored by parallel measurements of several types of responses.

If the above or other similar phenomena can be shown to account for at least part of the observed variance, then the relations between behavioral and physiological-biochemical models of drug action can cease to be antagonistic. In fact, the problem would not be any more than of knowing all that happens in the CNS when a particular drug, given various contingencies, leads to different types of response changes; in Oppenheimer's terms, this is a useless attempt to explain "everything." A more rational solution might be to employ consistent physiological-biochemical data accounting for a series of basic events (e.g. drug-induced changes at the level of different sensory, response, and reinforcement systems) as building blocks in behavioral models—a combination of reductionist and nonreductionist philosophies for the purpose of explaining "anything."

Some Behavioral Data Pertaining to the 5-HT Hypothesis of Tranquilizer Effects

It may appear surprising that some of the effects of 5-HT system drugs are analyzed in an appendix to the above discussion on barbiturates and benzodiazepines, at the expense of other more conventional topics such as the analogies and differences between antianxiety agents and neuroleptics. The fact is that two types of effects of benzodiazepines at the biochemical level have been emphasized in relation to their antipunishment effects, namely, (*a*) the inhibition of cyclic adenosine monophosphate phosphodiesterase (cAMPD) (178, 179), and (*b*) the interference with 5-HT

[4]Several provisional inferences with potential heuristic value might be drawn by reexamining the interactions between treatment and stimulus factors as a joint function of drug type, response type, and relations between stimuli, responses, and reinforcements (e.g. cues signaling gratis food vs cues signaling the availability of response-produced food in an intermittently reinforced schedule vs cues signaling nonreinforcement, etc; see, for example, 16–18, 27, 65, 67). No use has been made in psychopharmacology of some techniques and tentative models in the literature on autoshaping, which emphasize the variable balance between consequences of stimulus-reinforcement relations and consequences of response-reinforcement relations, as a joint function of cue, reinforcement, and response categories.

turnover (71). As concerns the former, the reader must be referred to a study of correlations between antipunishment and anti-cAMPD effects of various agents (178) and to the data showing an enhanced suppression and an antagonism of chlordiazepoxide effects in a CER test by a cAMPD stimulator (imidazol-4-acetic acid) (179). Regarding the latter, it has been reported that effects of benzodiazepines on punished behavior and on 5-HT turnover are maintained with repeated treatments, while tolerance develops to depressant effects and to drug-induced changes of noradrenaline turnover (71). Furthermore, several experiments have shown an attenuated suppression in conflict and in CER situations after treatment with a 5-HT–depleting agent (parachlorophenylalanine, PCPA) or with 5-HT antagonists (cyproheptadine, cinanserin, methysergide, 2-bromlysergic acid diethylamide) (71, 180–189), while the administration of 5-hydroxytryptophan (5-HTP) counteracted the antipunishment action of PCPA and of cinanserin (180, 181, 184, 189).[5]

Two types of arguments have been used against the hypothesis that central 5-HT systems have a major role in punishment suppression, and more or less directly, against the hypothesis that antianxiety agents act mainly by interfering with 5-HT turnover. First, one study failed to show an antipunishment effect of cinanserin in a situation in which chlordiazepoxide was quite active, while both agents antagonized the reduction of response rate caused by N,N-dimethyltryptamine (193). In this regard, several effects of 5-HT system agents on operant and instrumental responses maintained by positive reinforcement are far from being amenable to any simple explanation. In fact, a response depression has been obtained with a variety of drugs that cause different or even opposite biochemical effects, such as 5-HTP, several substituted tryptamines, PCPA, and 5-HT antagonists (194–199), while subthreshold doses of 5-HTP acquired depressant properties after pretreatment with PCPA (200). The same group responsible for the latter study showed a similar phenomenon with subthreshold doses of LSD-25 in animals with 5-HT depletion induced either by PCPA or by midbrain raphe lesions (201, 202).

A second line of criticism has denied both (*a*) that the available data show a parallelism between 5-HT depletion and alleviation of punishment suppression by PCPA, and (*b*) that the measurements and statistical procedures used in previous studies could demonstrate a reliable antipunishment action of the drug (203). Additional experiments with the same agent yielded apparently negative results (203).

While the above controversy cannot be solved in the present context, it can be underlined that several effects of 5-HT–depleting drugs or lesions are quite different from those observed after benzodiazepines. It is true that some of these changes, such as the facilitation of avoidance response in several shuttle box and lever-press studies (204–210), are amenable to an explanation based on a reduction of punish-

[5]In one of these studies (188) an attenuation of punishment suppression was also observed with lysergic acid diethylamide (LSD-25), while other studies using either concurrent positive reinforcement and punishment (190), or previous or concurrent punishment of an active avoidance response (191, 192) seem to deny the generality of the antipunishment action of this drug. In any event, most of the complex effects of LSD-25 must be left outside of the present discussion.

ment suppression (see the section on behavior maintained by negative reinforcement.[6] However, several components of the 5-HT depletion syndrome (e.g. hyperreactivity) (215–218) create a wide area of nonoverlap with the tranquilizer syndrome.

The above situation suggests that simpler models of drug action, which were originally endowed with considerable heuristic value, should now be replaced by multifactorial working hypotheses. These need not reject the provisional assumption that some apparently similar effects of tranquilizers and of 5-HT system agents can be induced by similar mechanisms, while other explanations should be sought for several effects taking place in different directions. Attention can be focused here on some methodological problems, even though they belong to areas not included in the present review. In the first place, there is an obvious disproportion between studies of complex behaviors using intracerebral treatments or lesioned animals that have been carried out respectively with noradrenergic, dopaminergic, and cholinergic stimulants and blockers and with tranquilizers and 5-HT depletors and antagonists (219–223). In the case of the former agents, several qualitative and quantitative differences in the behavioral effects, depending on treatment or lesion site, have indicated that the complex syndromes obtained by systemic treatments can be separated into increasingly well-defined components. Another methodological problem is pointed out by the considerable time lags that usually separate the obtention of "expected" effects of one or the other drug and that of "paradoxical" effects of the same agent. This situation applies to several data discussed in previous sections, inasmuch as the enhancements of low rates of schedule-controlled behavior, of punished behavior, and of avoidance behavior have generally been obtained at a later time, and with lower doses, than depressant effects. As concerns other areas, the joint study of floor and ceiling phenomena and of nonmonotonic dose-response relationships has been recently extended to aggressive responses and to "predatory" behaviors such as mouse and frog killing by rats. Several important differences have been pointed out between the enhanced intraspecies aggression obtained with relatively low doses of tranquilizers, on the one side, and the indirect facilitation of aggression (mainly via interactions with other agents) and the enhanced interspecific killing obtained with 5-HT depletors, on the other side (224, 225). The fact remains that the use of situations that eliminate floor and ceiling effects and of nonmonotonic dose-response functions can still have a considerable potential in an analysis of the mechanisms of action of agents with partially overlapping profiles.

[6]As with most avoidance-enhancing drugs, negative data (presumably due to ceiling effects), or even opposite (depressant) effects were obtained when using pretrained animals with high response base lines (211, 212). Furthermore, the fact that the enhancing effects of raphe lesions on two-way avoidance are paralleled by a depression of one-way avoidance (205) is in line with the above interpretation—at least according to much literature on CNS lesions such as that reviewed by McCleary (213). On the other hand, the available evidence does not allow direct comparisons between the effects of 5-HT system drugs (204, 214) and those of barbiturates and benzodiazepines in passive-avoidance tests other than those that measure the suppression of operant or consummatory behaviors.

BEHAVIORAL TOXICOLOGY

Although behavioral toxicology has only recently gained status as a semiautonomous discipline (226–232), several lines of research in this area have been firmly established for fairly long periods of time. In fact, with more space available one could refer (*a*) to much work carried out in animal and human subjects in order to assess the adverse behavioral effects of alcohol, tobacco smoke, and several drugs of abuse; (*b*) to a great deal of data on behavioral effects of nutritional or hormonal deficits and imbalances; (*c*) to several investigations attempting to establish animal models of human diseases marked by disturbances of mental development (e.g. phenylketonuria); and (*d*) to an increasing number of studies dealing with behavioral changes induced by ionizing and nonionizing radiation, hypoxia, carbon monoxide, several compounds used in the manufacturing industry, pesticides, air and water pollutants, food additives, and so forth. The present section, however, must leave out most of the studies using behavioral measurements largely as convenient dependent variables, which can be easily located via computerized indexing and abstracting services, and can be handled without trouble also by investigators who do not specialize in behavioral research. Considered here are mainly those data that have remarkable methodological interest, and at the same time require an understanding of behavior organization beyond the general information level of the nonspecialist.

Some Consequences of Stimulus Functions of Drugs and Chemicals

In recent years an increasing number of behavioral investigations on stimulus functions of various agents have been carried out by pharmacologists and psychologists, sometimes without any direct reference to the toxicological implications of the results obtained. Stimulus functions of physical and chemical agents are usually subdivided into discriminative (CS), unconditioned (UCS), and reinforcing functions (46). The term *CS function* implies that changes in the "internal state" caused by a treatment can become a signal controlling one or the other behavioral output, by taking up a role in response modulation similar to that of conventional stimuli of one or the other modality. While the reader must be referred to the available reviews for more systematic information (46, 47), a limited discussion is in order here to show both the difficulties encountered when interpreting the results in this area, and the relevance of state-dependence phenomena for drug abuse and for the understanding of dissociative side effects of drugs.

The studies so far carried out have indicated that any agent can acquire CS functions in experiments in which different response outputs must be emitted to meet reinforcement requirements, if the only available cue is a treatment administered before a particular session, for example, food obtained or shock avoided by turning to the left, or by pressing the left lever, after the administration of a given drug, and by going to the right, or by pressing the right lever, after administration of saline. However, when turning to comparisons between different drugs, or between different doses of the same drug, considerable attention must be given to the particular paradigm in which an apparent similarity, or an apparent difference, has

been observed. For example, several experiments by the same group of investigators showed that (*a*) rats trained in two-lever tasks with alcohol versus placebo gave the "alcohol" response when tested with pentobarbital; (*b*) rats trained in similar tasks to discriminate pentobarbital from placebo gave either the "placebo," or the "pentobarbital" response when tested with alcohol, depending on the reinforcer; and (*c*) rats could be taught to use one of the levers when treated with pentobarbital, and to use the other lever when treated with alcohol (233). The overall conclusion is obviously that the stimulus properties of the two agents have some element in common (the *a* and part of the *b* results). At the same time, however, one can be confident that the two states are discriminable from each other (the *c* result). Finally, the presence or absence of generalization from one to the other set of internal stimuli generated by the two agents must depend on which component of a given set has gained control of behavior during the original discrimination training —the *a* and the *b* results; for additional examples of these asymmetrical transfer phenomena see also (234). It goes without saying that any attempt to draw a conclusion from any one of the three types of data summarized above would have led to a considerably distorted picture of the analogies and differences between the pentobarbital and the alcohol states.

This and much other evidence shows that the results of experiments on state dependence are best understood by making reference to the basic facts of conventional experiments on discrimination and stimulus generalization, up to and including those concerned with psychophysical measurements. In fact, the variable data in *a* and *b* are similar to those that can be obtained when subjects are taught to discriminate between stimuli A and B (corresponding to different response-reinforcement contingencies), and then tested to see whether a third stimulus (X) will elicit an A- or a B-type response, or a mixture of the two. Assume now that this experiment has shown that X elicits an A-type response in one or more paradigms. It cannot be concluded from this that A and X are not discriminable from each other; such a conclusion can be had only by training with different response-reinforcement contingencies in the presence of A and X. Furthermore, if a first attempt fails, it cannot be inferred that A and X have a substantial identity (psychophysically speaking). In fact, the literature abounds with data showing that stimuli known to be discriminable from each other cannot be used, or are used only with considerable difficulty, as differential signals in particular discrimination tasks. Therefore, only a gradual accumulation of negative findings in different tests in which two states are pitched against each other can eventually demonstrate that the states themselves are indistinguishable.

Other data on state dependence have been obtained by imposing shifts from a treatment to a no-treatment state and vice versa (or from one treatment to another and vice versa) in conventional tasks that can be learned without relying on drug-induced stimuli. These data show that transfer, or no transfer (dissociation), of behavior acquired in a given state to a different one depends on complex interactions between treatment and test factors. For example, T-maze avoidance studies showed several years ago that transitions from the phenobarbital to the no-drug state, or vice versa, had an adverse effect on response initiation (start time), but not on response

execution (running time), nor on response choice (proportion of correct turns) (235). Other experiments with the same drug pointed out a successful transfer in either direction of an immobility (freezing) response, but not of an active escape response (236). Finally, it was shown that in particular conditions a state change can facilitate discrimination reversal as discussed previously (evidence for state dependence), even in the absence of a retention deficit with respect to the original discrimination (evidence against state dependence) (48).

In theory, several types of phenomena could account for the contrasting consequences of state changes as a function of test factors, but unfortunately, no single set of interactions obtained with a particular agent has so far been fully explained. Some possibilities have little to do with stimulus functions per se; that is, it is conceivable that general behavioral changes due either to treatment initiation, or to withdrawal of an agent to which the organism has been accustomed, can have widely differing consequences on the transfer of various types of responses from one state to another. On the other hand, by taking recourse to conventional discrimination data one could show that response control can come more under one, or more under the other type of stimulus, depending on the characteristics of the task. In other words, when the experimenter provides a set of relevant (conventional) stimuli, and also superimposes another set of stimuli (those derived from the drug-induced changes of the *milieu intérieur*), he cannot foresee whether or not elements from the two sets will be used as compound signals, and if they are, which particular aspects of the behavior will show dissociative phenomena. Conversely, state dependence in tasks learned on the basis of relevant treatment cues (chlordiazepoxide versus placebo) has been shown to vary as a function of the exteroceptive stimuli superimposed on the internal cues (237, 238).

No great efforts are required to explain the toxicological implications of the various types of findings. The greater or lesser discriminability of a drug state, as well as the greater or lesser analogies between two or more drug states (including different doses of the same drug), have obvious relevance in the analysis of abuse phenomena, and should be given increasing attention when assessing the effects and side effects of psychotropic drug treatments (or treatment changes). Furthermore, with some remarkable exceptions (concerning, e.g. alcohol), little is known about the factors that determine whether or not behaviors acquired in particular states are transferred to other states in human subjects. Finally, no attention has been so far given to possible dissociative effects of a variety of chemicals to which individuals can be exposed for variable periods of time, for example at work, but not elsewhere; or at home, but not elsewhere.

UCS and reinforcing functions of various agents have no smaller interest than CS functions, although some of them are so well known (and well reviewed) that they need not be discussed in detail. This applies to positively reinforcing properties of various agents, which have been extensively investigated by preference and self-administration tests in several species, in the framework of research on abuse phenomena (239–244). Furthermore, several studies on conditioning of drug treatment and of drug withdrawal effects have been carried out in an attempt to separate "physical" and "psychic" aspects of drug dependence (46, 241, 243, 244a). While

a few of these experiments, not pertaining directly to the abuse problem, will have to be mentioned later, some attention must be given here to several recent results concerning either behavior suppression by treatments with aversive properties, or escape-avoidance behaviors established and maintained with treatments used as the UCS.

In addition to conventional tests carried out with preference-rejection paradigms, recent research has increasingly exploited the so-called Garcia paradigm, which allows the study of conditioned aversion phenomena ("bait shyness") (245, 246). In fact, when particular cues (mainly gustatory ones in nonvisual animals, such as rodents, and visual ones in species that select food mainly on the basis of visual cues, such as diurnal birds) are associated with an experience of "malaise" or "illness" caused by a physical or chemical agent, they can acquire suppressant properties similar to those of a conventional CS in a classical (CER) paradigm. Furthermore, conditioned suppression can develop in spite of CS-UCS delays much longer than those that allow classical fear conditioning with conventional exteroceptive signals (e.g. tones or lights) and conventional UCS (e.g. painful shock). Few problems arise with the fact that conditioned aversions are easily established (*a*) with ionizing radiations, and with substances such as cyclophosphamide and lithium, at doses sufficient to cause overt signs of physical illness (245), and (*b*) with subtoxic doses of agents that are well known for the "unpleasant" quality of the experience they produce, such as apomorphine (245) and antimuscarinics (247, 247a). Equally, one can easily understand why positively reinforcing and punishing properties of the alcohol (247a, 248–250) and of the morphine (247a, 248, 251) experiences should be related to each other in a complex fashion. Other recent results however, were quite unexpected. This applies, to conditioned aversions obtained with doses of lithium (252), chlorpromazine (247), and benzodiazepine derivatives (247, 247a, 248) either within or not much above the therapeutic range, and with doses of amphetamine within the self-administration range (247a, 253–258). On the other hand, the conditioned aversions recently obtained with several barbiturates and with the nonbarbiturate hypnotic methaqualone (247a, 258a) are in contrast with previous negative results concerning one of the compounds [phenobarbital (247)]. Furthermore, negative results have been obtained with the tricyclic antidepressant imipramine (247), while the data so far available on cannabis derivatives (247a, 259–262) appear to be insufficient to conclude for a specificity, or a nonspecificity —with respect to doses endowed with conventional psychotropic effects (263, 264) —of the aversions obtained.

Although with the present state of knowledge any classification must be provisional, and perhaps arbitrary, it can have at least heuristic value to separate aversive properties of therapeutic agents that are seldom, if ever, self-administered (such as chlorpromazine and lithium) from those of agents that are often self-administered and lead to abuse phenomena (ethanol, morphine, amphetamines, hypnotic-sedatives, and tranquilizers). The former appear to have considerable relevance in a rational risk-benefit analysis, if the goal of a therapy must be that of maximizing returns, while minimizing both conventional side effects and subjective disturbances. The latter have relevance both from the above viewpoint, for example, when consid-

ering the extensive therapeutical applications of tranquilizers, and from the viewpoint of abuse phenomena. Within this category are most of the results that are hotly debated, since similar phenomena are ascribed to widely differing mechanisms by various authorities. For example, a more detailed analysis of the literature on behavior suppression by amphetamine (253–258) could show that these phenomena are ascribed to the development of genuine conditioned aversions by some experimenters, and to a conditioning of the anorexigenic effects of the drug by others. Furthermore, the data showing a suppressant action on ongoing operant behavior of stimuli previously associated with chlorpromazine or LSD-25 have also been interpreted as the consequence of a conditioning of drug-induced changes, rather than of punishment suppression (265, 266). Finally, some drug profiles can be quite complex with respect not only to induction of both self-administration and conditioned aversions at similar doses, but also to their influences on negatively reinforcing properties of other agents. For example, chlordiazepoxide was found to attenuate conditioned aversions induced either by amphetamine or by lithium (254, 267), which is obviously in agreement with the antipunishment properties measured in conventional tests.

The provisional conclusion must be that the relations between positively reinforcing, punishing, and other properties of any given agent can be clarified only by a further extension of the available tests. Traditional preference-rejection tests, self-administration tests, and conditioned aversion (Garcia-type) tests have recently been joined by choice procedures using conditioned reinforcers, that is, exteroceptive stimuli previously paired to different drugs, or to different doses of the same drug (267a), and by escape-avoidance techniques allowing one to assess whether an animal tolerates, or escapes and avoids, scheduled infusions. The combined use of these and of self-administration techniques has already yielded a series of interesting results. For example, monkeys made dependent on morphine by treatments imposed by the experimenters escaped and avoided nalorphine and naloxone infusions, while monkeys made dependent in a self-administration paradigm went on self-administering nalorphine in substitution tests, even though this precipitated a severe abstinence syndrome (268). When the studies were extended to animals without prior addiction, the results clearly separated several treatments that were accepted (naloxone, cocaine, codeine, pentazocine, and propiramfumarate infusions) from others that were escaped and avoided (nalorphine and cyclazocine infusions) (269); for additional evidence on the mixed positively reinforcing and punishing properties of narcotic antagonists see (270, 271). Furthermore, a recent study showed a contrast between the acceptance of pentobarbital up to a fairly high dosage level (0.1 mg/kg per infusion) and escape-avoidance of both chlorpromazine (down to 0.005 mg/kg per infusion) and LSD-25 (down to 0.001 mg/kg per infusion) (272). Finally, an indirect confirmation of the results on chlorpromazine aversiveness obtained in Garcia-type and escape-avoidance tests was provided by self-administration studies, using monkeys that performed in an operant (FR) schedule with cocaine as the reinforcer. In fact, substitution tests yielded amphetamine and morphine rates higher than saline rates, imipramine rates comparable to saline rates, and chlorpromazine rates significantly lower than saline rates (273).

Selected (Mainly Developmental) Data on Psychotropic Drugs, Pesticides, Food Additives, Mercury, and Lead

This section deals with some of the effects of prenatal or early postnatal treatments with psychotropic drugs, and comments upon some results showing that exposure of immature organisms to various chemicals can lead to behavioral changes that are not usually obtained by treating adult animals. Several studies conducted in the sixties, which have been reviewed in (274–278), showed various types of deviations from normal behavior development after pre- or postnatal administration of psychotropic agents. More recently, several suggestions have been made concerning biochemical changes underlying altered behavior maturation, especially regarding the effects on catecholamine and indole amine metabolism of early exposure to amphetamines (279–281), chlorpromazine (280, 281), haloperidol (282, 283), LSD-25 (284), ethanol (285), and PCPA (286). Other studies have either attempted a better definition of treatment variables or investigated interactions of considerable interest between treatment and other factors. For example, the data on the effects of pre- and postnatal morphine in the rat were extended by results showing opposite effects of different dosage levels on avoidance acquisition at a later time—facilitation after smaller doses, and depression after higher doses (287). Several experiments using prenatal amphetamine treatments showed correlations between enhanced activity, enhanced active avoidance, and impaired passive avoidance (279, 288, 289), while postnatal treatments with an enhancing effect on neonatal locomotor activity did not modify adult two-way avoidance learning (289a). Previous work on adverse effects of prolonged postnatal treatments with phenothiazines on later avoidance in the rat were also extended in several directions. First, the use of shorter (6-day) trifluoperazine treatments showed that the avoidance deficits were the consequence of cumulative damage, rather than of a selective effect during particular critical periods (290). Second, depressed avoidance was observed in the first and second generation obtained from females that had received phenothiazines postnatally (291–294). One of these studies using a cross-fostering control showed that nursing of the young by dams that had previously received postnatal phenothiazine treatments was not necessary to obtain depression of avoidance (294). Finally, one experiment with 0.16–0.33 mg/kg of trifluoperazine administered daily for 25 days yielded nonmonotonic dose-response relationships with respect to avoidance performance of the offspring of females that had received postnatal treatment (293). These data are highly suggestive of multiple mechanisms of action at least in part in opposition to each other, because cross-generational effects on avoidance were larger after lower doses, than after higher doses. On the other hand, impairments of behavioral development including avoidance deficits have also been obtained in recent years by treating neonate rabbits with other types of neuroleptics [butyrophenones, pimozide; see (294a) and other papers by the same group quoted therein].

Another group of investigators used prenatal chlorpromazine treatments inducing a greater susceptibility to seizures at 30 days of age, and higher avoidance abilities at 90 days. In this instance the cross-fostering procedure showed that at least part of the changes occurred in animals not exposed in utero, but nursed by

previously treated mothers (295). On the other hand, cross-fostering controls indicated that the effects on the offspring of Δ^9-tetrahydrocannabinol administered at a fairly high dose to pregnant rats (10 mg/kg daily for three days) (retarded growth, reduced rearing and grooming, retarded development of cliff avoidance and of visual placing reflexes) were due entirely to prenatally suffered damage (296). Similar procedures, however, do not seem to have been employed when dealing with more subtle changes induced by prenatal cannabis exposure, for example, the retardation of learning in a Lashley III maze (297). Finally, several studies using postnatal strychnine (298–301), methamphetamine (302) and PCPA (286), and prenatal imipramine (303) indicated that the effects of drugs on behavior development can depend on the characteristics of the environment in which the animals are raised.

In summary, the results so far obtained suggest that pre- or early postnatal treatments by psychotropic agents can influence behavior development in widely differing ways, ranging from direct effects on brain mechanisms at the time of exposure to altered mother-offspring interactions at a time when the drug is no longer present. This evidence places a considerable burden on future experimentation, because it shows that it is not enough to consider the interactions between the most obvious factors such as species, type of drug, doses, time and duration of exposure, behavioral tests, and so forth. As a consequence, there arises the need for a standardization of procedures allowing the assessment of indirect mechanisms of action (e.g. prenatal and postnatal maternal effects) in order to ensure that the data obtained in different laboratories are amenable to direct comparisons.

The literature on the behavioral effects of pesticides shows that organophosphate and carbamate compounds have been used very extensively both in toxicological investigations, and in studies of biochemistry-behavior correlations exploiting the well-known effects of the compounds on central cholinergic systems. For an overview of this subject see (304), and for more recent data and references on tolerance mechanisms see one of the latest papers by the most active group in this area (305). Comparatively speaking, behavioral data on organochlorine compounds are much less extensive than those on anticholinesterase agents. However, the concern created by the persistence in the environment of agents such as DDT has led to a number of studies of the behavioral effects of organochlorine insecticides in fish [see recent data and references in (306)] and to a multi-year research project using behavioral (mainly discrimination) and electrophysiological measurements in sheep (307). Furthermore, ready access to the literature on behavioral and electrophysiological changes induced by organochlorine compounds in several laboratory species is provided by a recent review (307a) and by several recent papers reporting changes in activity, avoidance, discrimination, operant and maze behavior, maternal and aggressive behavior, and electrical activity (308–315).

A survey of the studies concerned with early treatments by pesticides shows that few cues are presently available to understand the mechanisms by which these compounds affect behavioral development. In fact, a series of experiments carried out in mice by one investigator (although with different co-workers and in different laboratories) showed changes in maturation of seizure sensitivity after prenatal DDT, aldrin, chlordane, and parathion, while prenatal chlordane, but not DDT or

parathion, led to later enhancements of open-field activity, and prenatal chlordane or DDT, but not parathion nor aldrin, retarded avoidance behavior (316–321). T-maze performance of mice has also been found to be altered by pre- and neonatal exposure to DDT (322). On the other hand, postnatal exposure to an anticholinesterase fungicide (maneb) had correlated effects on activity (depressed) and passive avoidance (facilitated). Response changes per se, however, were not sufficient to account for all the effects observed, since active avoidance was also facilitated (323).

Some recent findings—including alteration of reproductive functions in rats and mice after prenatal or neonatal exposure to DDT, or to some of its analogs, or to polychlorinated biphenyls (PCBs) (324, 324a); the altered development of ambulation and rearing in rats after prenatal administration of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T, with less than 1 ppm of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) (325, 325a)—confirm the suspicion that the weak estrogenic action of several organochlorine compounds might have a role in behavior modification by early treatments. In fact, all reproductive and nonreproductive behaviors so far mentioned are known to be influenced by hormonal treatments during critical periods.[7] On the other hand, biochemical studies on DDT and chlordane have shown complex changes in the metabolism of acetylcholine, noradrenaline, 5-HT, and amino acids in the brain (307a, 326–330), which provides a basis for a more thorough comparison of the mechanisms of action of organochlorine compounds with those of better-known agents.

Although this discussion cannot be extended to a wide range of substances that can enter the organism via foods and beverages, recent studies using nitrites (331), butylated hydroxyanisole and butylated hydroxytoluene (332), cyclamates (333, 334), and monosodium glutamate (MSG) (335–337) can be mentioned to point out the growing concern for developmental changes induced by various types of agents. These studies have sometimes provided interesting cues concerning possible mechanisms of action, as shown by some of the data on MSG. For example, the obesity-hyperactivity syndrome observed after neonatal exposure of mice (335) should be confronted with the irreversible inhibition of pituitary prolactin and growth hormone secretion induced by similar treatments in the same species (338), again leading to speculations about possible interferences with "organization" of CNS systems by hormonal influences during critical periods of development. Also in this instance the available data suggest a large difference in sensitivity between developing and mature organisms, as exemplified by the transient and apparently nonspecific depression by large doses of MSG of fixed ratio and of avoidance response in adult rats (339, 340).

In a discussion of mercury compounds, the behavioral and electrophysiological studies dealing with exposure in adulthood, or during relatively late postnatal periods, for example, those reported or discussed in (341–356) should again be

[7]Note, however, that the results have been often contradictory ones, even in the hands of the same investigators (325, 325a), and also that 2,4,5-T treatments were given during the first half of pregnancy (325, 325a), that is, too early for those "organizational" effects on reproductive functions and behavior that are usually described in the literature on hormones.

contrasted with those using pre- and early postnatal treatments (231, 357–362). The results obtained by the former approach have shown a variable sensitivity to mercury treatments of the tests used, as indicated by the comparisons carried out in the Rochester research project (354–356). Furthermore, some experiments have pointed out that the intake of diets contaminated by mercury can be reduced by aversion phenomena (342, 344). These, however, do not seem to afford an efficient protection, as indicated by the well-known data on humans and animals that pertain to the Minamata, to the Iraq, and to other accidents. On the other hand, the developmental studies mentioned above, which used both rodents and birds, revealed a uniformly high sensitivity of immature organisms. Furthermore, these results include an impressive series of different phenomena, ranging from deficits observed relatively early in life [e.g. the changes in the neonatal sequence of development in rats, involving eye opening and neuromotor coordination (360)] to the effects appearing only at a much later time, such as the general debilitation and the gross neurological changes observed in mice about the end of the first year of life (361, 361a).

Finally, similar research trends have made their appearance in the analysis of behavioral effects of lead. Most of these studies have used postnatal exposure of rat and mouse offspring via the milk of treated dams, sometimes combined with later treatment of weanlings by different dietary levels of lead compounds (363–369). Although no in-depth discussion of the results is possible here, several points deserve to be emphasized. First, the available data have convincingly shown a much higher sensitivity of immature, than of adult animals; for consequences of treatments given later in life see (368, 370–372). Second, a recent dose-response study has revealed a separation of gross neurological disorders caused by higher doses from more subtle behavioral changes following exposure to lower doses (mainly hyperactivity) (364). Third, the lead intake via contaminated food, which normally leads to aversion phenomena, was found to be increased by the reduction of dietary calcium (373), a finding with obvious implications with respect to lead pica in humans. Fourth, the offspring from female rats receiving lead acetate during lactation showed both an enhanced fluid consumption and a greater aversion for lead acetate solutions than did the control offspring (364a). Fifth, rats made hyperactive by early exposure to lead showed paradoxical changes after drug treatments, namely, a further enhancement of activity levels after phenobarbital, and a reduction of activity after *d*- or *l*-amphetamine and other stimulants (367, 367a, 369). Amphetamine, however, maintained its well-known ability to enhance low rates of avoidance responses (369). Finally, a series of studies was carried out in sheep by the Iowa behavioral toxicology program (374–377). Not only did these experiments confirm the greater liability to damage in the pre- and early postnatal stages, than in adulthood; but also, they pointed out that impairments of behavioral development can take place with lead blood levels below those considered acceptable by EPA for pregnant women (up to 30 μg/100 ml) and for children (up to 40 μg/100 ml).

Since a fairly optimistic attitude has been maintained throughout the present discussion, concerning the progress made by behavioral toxicology in recent years, a final caveat is in order here. In fact, most of the studies mentioned above have

followed, rather than preceded, the demonstration of adverse effects in humans, while satisfactory criteria for extrapolation from animals to man in previsional experiments have not been established. Given the complexity of developmental studies, it is understandable that dose-response experiments should have been the exception, rather than the rule. Furthermore, if one considers the thresholds that have been measured (or if one even optimistically assumes that thresholds will be found to be immediately below the effective dosage levels in experiments with a single treatment schedule), one can expect considerable trouble at the moment of deciding on safety factors. In fact, nonbehavioral previsional toxicology uses safety factors for the extrapolation from animals to man that are generally about one hundred. One could easily show at this point that maximum allowable levels of exposure for most agents mentioned here would have to be brought down to a near zero level in the case of expectant or nursing mothers and of young children, if the conventional procedure were extended to the results of studies of behavioral development.

GENERAL DISCUSSION AND CONCLUSIONS

A more general evaluation of the state of the art of behavioral pharmacology in the midseventies can emphasize both the risks and the benefits of an increasing complexity of working hypotheses that are used when dealing with drug-behavior interactions, with both explanatory and heuristic purposes. In fact, the diminishing returns obtained by the use of simpler models inevitably leads to serious problems of communication not only among behavior specialists and neurophysiologists, biochemists and clinicians, but also among behavioral pharmacologists with different orientations. This review tries to compensate at least in part for the minimal cross-referencing between studies using a functional approach and studies centered on assumed processes and mechanisms. At the opposite end, several developments deserve to be classified as potential, if not yet actual, benefits. In fact, it is increasingly realized that in this, as in other areas of the biological sciences (378), reductionist ("molecular") and nonreductionist ("molar") approaches need not to be pitched against each other, since they can be shown to be complementary (see the section on the nature of drug-behavior interactions).

Thus the philosophies underlying the extrapolations from the animal laboratory to the clinic are being gradually revised, and the relative roles of the two types of research are defined more clearly.

Animal psychopharmacology and behavioral toxicology, although necessarily subdivided into several specialized areas, appear to be at their best when not hampered by arbitrary distinctions between effects and side effects of the agents studied, nor by chicken-and-egg questions about which level of explanation is most appropriate. In recent years they have attempted to provide sophisticated interaction models that take into account several phenomena of increasing complexity, including differential changes in various portions of species-specific repertoires, changes in stimulus reactivity, changes depending on various response-reinforcement relationships, rate-dependence phenomena, and stimulus functions of drugs. Even though the latter have been given only a minimum of attention in the section on behavioral tox-

icology, they can be used to show how the extremes of a continuum are, in reality, quite close to each other. In fact, the study of discriminative functions of drugs fulfills both the need to know more about critical stimulus factors in conditioning and learning (or, if preferred, in behavior control), and the need to understand dissociative side effects of psychotropic agents as well as the "substitution potentials" of various drugs of abuse. Correspondingly, the study of positively and negatively reinforcing functions fulfills both the need to clarify the physiological-biochemical substrates of reinforcement processes (or, in a functional analysis, equivalence and nonequivalence phenomena with different reinforcers), and that of understanding abuse phenomena as well as aversive side effects of therapeutic agents. As pointed out in the behavioral toxicology section, positively reinforcing and aversive properties are often found to coexist in animal experiments; therefore, one cannot expect to obtain simple answers when complex biological factors and even more complex social-cultural factors interact with each other in humans.

Several other examples could be drawn from the literature of behavioral pharmacology and toxicology to show the increasing need for strict relations between the basic and the mission-oriented aspects of any given problem. In the fifties the uneven development of appropriate interactions and feedbacks between research in reproductive and developmental biology and research on desired and undesired effects of drugs and chemicals led both to remarkable successes (e.g. the development of oral contraceptives) and to dramatic failures (e.g. thalidomide). In the seventies, it appears that the effort to understand the basic facts of behavioral development, as well as their physiological and biochemical substrates, goes in hand with remarkable efforts to assess the risks of the exposure to potentially noxious drugs and chemicals during critical maturation periods. The coming years will undoubtedly be marked by much uneasiness. In fact, the right questions have come to the surface, while appropriate answers to these questions are far from available. This is tantamount to affirming that both type I and type II errors can be made in large numbers at the operational level.

In any event, a few examples and general comments cannot suffice to clarify the complex relations between animal research and human applications in the realm of psychotropic drugs and other chemicals that affect behavior. Some may regret the pioneer age when terms such as *antiavoidance* and *antipsychotic,* or *anticonflict* and *antianxiety,* were almost synonyms; or when limited data on the general toxicity of a new agent were deemed to suffice for the completion of a risk-benefit analysis. A more realistic and responsible approach cannot be based solely on an increasingly broad range of previsional studies in animals. In fact, the value and the limits of extrapolations from animals to man can be thoroughly assessed only with the help of a much more extensive knowledge of basic analogies and differences between mechanisms than what is presently available. Animal psychopharmacologists and behavioral toxicologists have shown that, on the average, different species can vary with respect to behavioral changes induced by various agents more than they vary with respect to other types of changes—a logical consequence of the fact that behavioral specialization is both a "final common path" in adaptation to different environments, and an essential mechanism in the evolution and isolation of species.

However, the problems encountered when drawing comparisons between animal species are dwarfed by the inordinate proliferation of interacting factors in the human species, as shown by the apparently irreconcilable opinions on the reliability and meaning of one or the other type of data (379), and even more by the conflicts between judgments of value (380–383).

ACKNOWLEDGMENTS

This review is part of a program in experimental psychology and behavioral pharmacology sponsored jointly by Istituto Superiore di Sanità (ISS) and by Istituto di Psicologia, Consiglio Nazionale delle Ricerche (IP-CNR), Roma, Italy (1969 to date). The author wishes to acknowledge the help and advice received from Dr. G. L. Gatti (ISS) and from Dr. Marina Frontali (IP-CNR).

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